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Top-Down Control-Signal Dynamics in Anterior Cingulate and Prefrontal Cortex Neurons following Task Switching

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SUMMARY

The prefrontal cortex (PFC) and anterior cingulate cortex (ACC) have both been implicated in cognitive control, but their relative roles remain unclear. Here we recorded the activity of single neurons in both areas while monkeys performed a task that required them to switch between trials in which they had to look toward a flashed stimulus (prosaccades) and trials in which they had to look away from the stimulus (antisaccades). We found that ACC neurons had a higher level of task selectivity than PFC neurons during the preparatory period on trials immediately following a task switch. In ACC neurons, task selectivity was strongest after the task switch and declined throughout the task block, whereas task selectivity remained constant in the PFC. These results demonstrate that the ACC is recruited when cognitive demands increase and suggest a role for both areas in task maintenance and the implementation of top-down control.

INTRODUCTION

A remarkable aspect of primate behavior is the ability to switch rapidly between different tasks. Cognitive flexibility of this type allows humans and animals to successfully cope with the demands of a swiftly changing environment and is an integral element of intelligent behavior. Anatomical and physiological studies have suggested that the prefrontal cortex (PFC) and the anterior cingulate cortex (ACC) are involved in this executive control (Duncan, 2001; Miller and Cohen, 2001). Both areas are closely interconnected (Bates and Goldman-Rakic, 1993; Paus et al., 2001; Wang et al., 2004), suggesting that they may be involved in similar cognitive functions. Indeed, functional neuroimaging studies have shown a strikingly similar recruitment of the PFC and ACC in a multitude of cognitive tasks, including response conflict, task novelty, working memory, episodic memory, and problem solving (Duncan and Owen, 2000). Several studies have attempted to dissociate the roles of ACC and PFC in cognitive control (Liston et al., 2006; MacDonald et al., 2000), but the relative contributions of these areas remain unclear. One hypothesis proposes that the PFC is involved in the implementation of task control, whereas the ACC is involved in conflict monitoring (Botvinick et al., 2001; Kerns et al., 2004; MacDonald et al., 2000; Miller and Cohen, 2001). According to this model, the PFC provides top-down bias signals to other brain areas that implement the task-appropriate mapping between inputs and outputs. In this conceptualization, the ACC detects conflict when a stimulus coactivates two competing response processes. This conflict signal then leads to an increase in the top-down control in the PFC that is necessary for the maintenance of task set. Although well supported by a large number of human fMRI studies, single-neuron studies in monkeys have failed to find conflict-related signals in the ACC (Ito et al., 2003; Nakamura et al., 2005). Instead, these studies have demonstrated a role of the ACC in performance monitoring with many neurons showing different activity between either correct and incorrect responses or rewarded and unrewarded behavior. A recent model proposes that the ACC does not signal conflict or error performance per se, but more general error-likelihood (Brown and Braver, 2005). According to this model, the ACC is activated when more cognitive control is required due to an increase in task demands. A common situation in which task demands increase is when subjects have to switch from one task to another, especially if the two tasks require competing stimulus-response associations.

Task switching is commonly considered to be an example of executive processing, and as such, a large body of psychological research has investigated this behavior in human subjects (Allport et al., 1994; Sohn and Anderson, 2001; Yeung and Monsell, 2003). Human fMRI studies have reported increased activation of the PFC and ACC on trials following a task switch (Liston et al., 2006; Woodward et al., 2006; Wylie et al., 2004). In addition, lesion and inactivation studies in monkeys have demonstrated impairments in task switching following both PFC (Dias et al., 1996) and ACC (Rushworth et al., 2003; Shima and Tanji, 1998) lesions. To investigate the unique

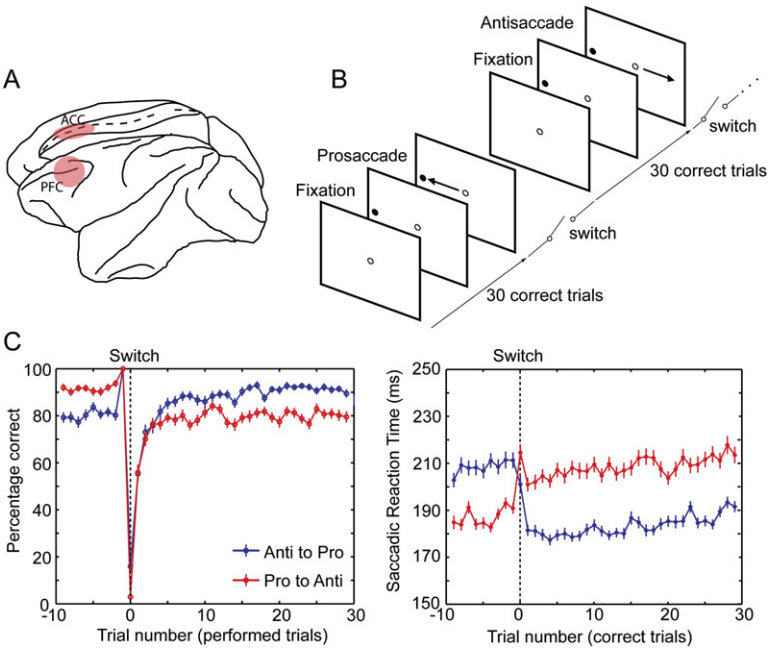

Figure 1. Brain Regions, Task, and Behavior

(A) Location of the prefrontal cortex (PFC) and anterior cingulate cortex (ACC).

(B) Schematic diagram of the switch task. Each trial began with the presentation of a small dot at the center of the screen that the monkey had to fixate. A stimulus appeared left or right, requiring either a prosaccade or antisaccade (arrows). No explicit instructions were provided. Monkeys had to acquire the current task rule by trial and error based on reward feedback that was delivered at the end of each trial. Prosaccade and antisaccade trials alternated after 30 correct responses.

(C) Performance (left) and saccadic reaction times (right) at task switch, averaged across all recording sessions and blocks from two monkeys. The first trial following a task switch is zero. Error bars indicate standard error of the mean. Figure labels for left and right panel are in the left panel.

contributions of the PFC and ACC to task maintenance and task switching, at the level of individual neurons, we recorded single-neuron activity in both the lateral prefrontal cortex (areas 9 and 46) and the anterior cingulate cortex (area 24c) (Figure 1A). Monkeys were trained to either generate a prosaccade or an antisaccade in response to a briefly presented peripheral visual stimulus (Munoz and Everling, 2004). The PFC and ACC have both been shown to be involved in performance of the antisaccade task by a number of studies (Condy et al., 2006; Everling and Desouza, 2005; Ford et al., 2005; Funahashi et al., 1993; Gaymard et al., 1998, 2003; Paus et al., 1993; Pierrot-Deseilligny et al., 2003; Ploner et al., 2005).The animals had to acquire the current task rule by trial and error based on the delivery or omission of reward after each trial. The tasks alternated without notice after 30 correct responses. In order to continue obtaining reward, the monkeys had to switch to the other task (Figure 1B). To successfully perform this paradigm, the animals had to engage and maintain the current task set over a block of trials and perform a task switch once the previous behavior was no longer rewarded.

Here we report different time courses of neural activity in the ACC and PFC consistent with the hypothesis that the activation of neurons in the ACC leads those in the PFC following a task switch.

RESULTS

Behavior

Figure 1C (left) shows the monkeys' performance before and after a task switch. Monkeys performed prosaccades at ~90% and antisaccades at ~80% before the task changed. The last trial before a switch was always performed at 100% because in our task design prosaccade and antisaccade blocks always alternated after the 30th correct trial in a block. Performance dropped to almost 0% for switches from prosaccades to antisaccades and to ~10% when switching from antisaccades to prosaccades. This is not surprising as the animals received no advance warning of the task switch and therefore continued to execute the previously rewarded behavior. Performance recovered rapidly following a switch, with the next trial already being at chance (50% correct) and the second trial after a task switch at ~70%–80%. Within five to ten trials, performance recovered to a level similar to that prior to the task switch. There was almost no effect of the task switch on the reaction times of prosaccades and antisaccades, with the exception of the first trial after a switch, which was associated with prolonged reaction times for pro- and antisaccades (Figure 1C, right).

Neural Activity

We recorded the activity of a total of 174 PFC neurons (124 in monkey R, 50 in monkey W) and 198 ACC neurons (95 in monkey R, 103 in monkey W) in two monkeys over the course of 87 experimental sessions. Many PFC and ACC neurons showed task-selective activity, which we defined as a difference in mean discharge rate between correct prosaccade and antisaccade trials. Examples of neurons with task-selective activity are shown in Figure 2. Consistent with findings in other cortical and subcortical brain areas (Amador et al., 2003; Everling et al., 1999; Everling and Munoz, 2000), many neurons exhibited different levels of activity between prosaccade and antisaccade trials prior to presentation of the peripheral stimulus. Here we focus on these task-related differences in preparatory neural activity. We compared the activity of each recorded

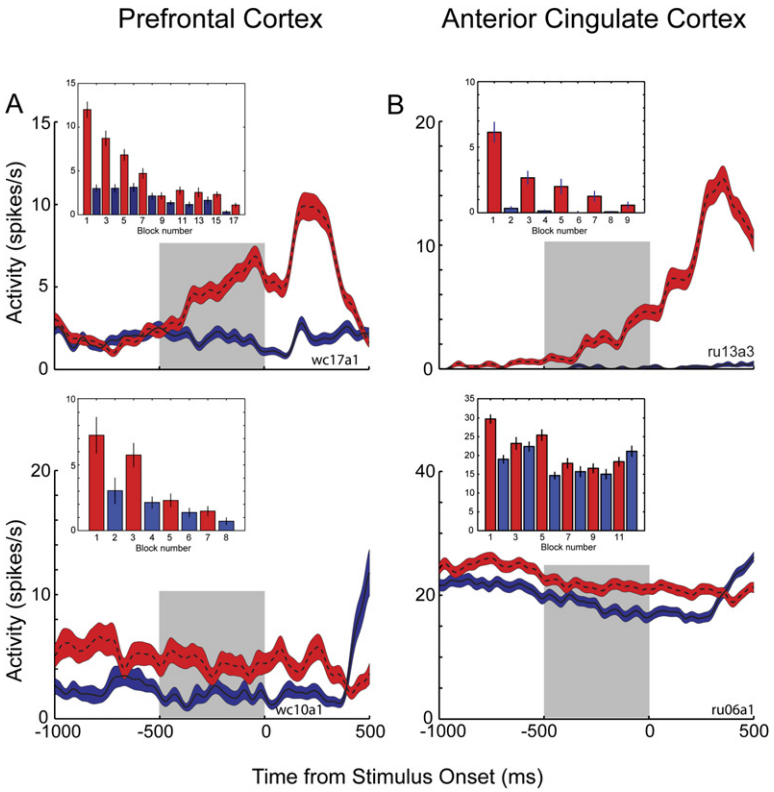

Figure 2. Examples of Single Neurons Showing Task-Selective Preparatory Activity

(A) Activity of a neuron in the prefrontal cortex showing a buildup of neural activity (top) and a neuron showing a more tonic activity during the instruction period (bottom). Both neurons were more active for antisaccades (red) than prosaccades (blue). Dashed and solid lines indicate mean spike-density functions, and envelopes indicate standard error of the mean. Spike density functions were computed by convolving spike trains with a 30 ms Gaussian activation function. All correct trials were used to compute these spike-density functions. The inserts demonstrate the reproducibility of task-selective differences in preparatory activity across multiple blocks for each neuron. The mean preparatory discharge rate (with standard errors of the mean) is shown for each block of trials (activity in the last 500 ms prior to peripheral stimulus onset, shaded area). Bars are color coded and indicate the task that is performed in each block. Colors match those of the spike-density functions.

(B) Same as (A) but in the anterior cingulate cortex.

PFC and ACC neuron between the two tasks during the preparatory period (see Experimental Procedures). In this initial analysis, 23% (46/198) of the ACC neurons and 30% (51/174) of the PFC neurons showed task-related differences in their preparatory activity (see Note 1 in the Supplemental Data available online). Consistent with a previous report (Everling and Desouza, 2005), we found no clear preference for either the prosaccade or antisaccade task in PFC neurons (23/51, or 45%, preferred antisaccades and 28/51, or 55%, preferred prosaccades; $p = 0.48$, χ^2 test). There was also no difference in the level of preparatory activity between prosaccade and antisaccade trials in the population of PFC neurons (Figure 3A, top; $p = 0.54$, paired t test). We also did not find a clear task preference for ACC neurons (28/46, or 60%, preferred antisaccades and 18/46, or 40%, preferred prosaccades; $p = 0.14$, χ^2 test). Conversely, the level of preparatory activity also showed no difference between prosaccade and antisaccade trials in the population of ACC neurons (Figure 3A, bottom; $p = 0.15$, paired t test).

The remainder of our analysis focused on the 51 PFC (36 from monkey R, 15 from monkey W) and 46 ACC neurons (26 from monkey R, 20 from monkey W) that showed significant differences in preparatory activity between prosaccade and antisaccade trials. To investigate the nature of these differences in preparatory activity, we quantified the relative time courses of task selectivity in the two areas by performing Receiver Operating Characteristics analyses (ROC, see Experimental Procedures). ROC values over the duration of a trial are shown for each individual PFC (Figure 3B, top) and ACC neuron (Figure 3B, middle). Some neurons exhibited task selectivity throughout the entire trial, while others exhibited selectivity only shortly before stimulus presentation. A comparison of the onset times of task selectivity did not reveal any differences between the sample of PFC and ACC neurons ($p = 0.24$).

Next, we investigated task selectivity as a function of the number of correct trials after a task switch for the population of PFC neurons (Figure 4A, left) and ACC neurons (Figure 4A, right). This comparison revealed striking differences in the onset and strength of task selectivity throughout a block of trials between neurons in the two brain regions. We could not account for these differences on the basis of behavioral performance, as the level of performance was similar across the recording sessions in which we recorded PFC and ACC activity (see Figure S1). The population of PFC neurons showed a constant magnitude of task selectivity throughout the block of trials. We tested the effects of trial number following a task switch on neural selectivity by dividing the task blocks into consecutive sub-blocks of five correct trials each (Figure 4B, left panel) and comparing the overall task selectivity between the six sub-blocks with a repeated-measures analysis of variance (ANOVA, see Experimental Procedures). This analysis revealed no differences in task selectivity throughout the block for PFC neurons [$F(5,250) = 1.0$; $p = 0.42$]. The population of ACC neurons, however, showed strong task

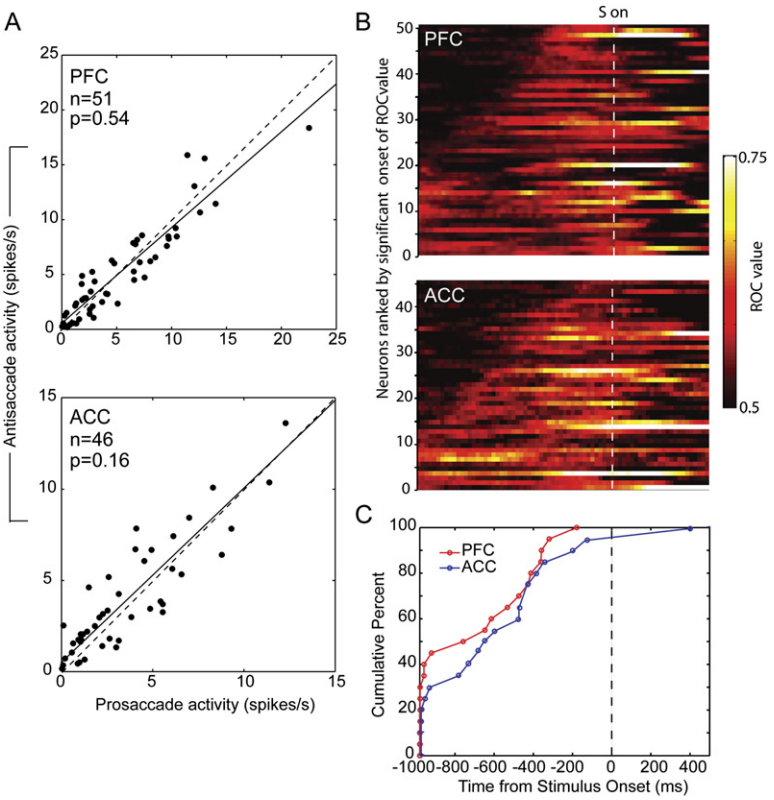

Figure 3. Task Selectivity in PFC and ACC

(A) Mean activities of individual PFC neurons (top) and ACC neurons (bottom) during the preparatory period (500 ms prior to stimulus onset) are plotted for prosaccades (abscissa) versus antisaccade trials (ordinate). Dotted lines indicate unity lines (slope = 1), and solid lines indicate least-squares fits.

(B) The time courses of task selectivity of PFC (top) and ACC neurons (bottom) were determined using sliding ROC analyses. Neurons were sorted by the onset of significant differences.

(C) Onset times of task selectivity for PFC (red) and ACC (blue) neurons. A larger proportion of PFC than ACC neurons showed early task selectivity (red line above blue line). Dashed lines indicate the time of stimulus onset. All data are based on correct prosaccade and antisaccade trials collapsed across all blocks.

selectivity immediately following a task switch, which then decreased throughout the block (Figure 4B, right panel). An ANOVA confirmed a significant main effect of sub-block following task switch on task selectivity for ACC neurons [$F(5,225) = 5.68$; $p < 0.0001$]. These differences in the neural activity between ACC and PFC neurons were also evident in single neurons (Figure S2) and in their population activity (Figure S3). Both monkeys showed a similar pattern of task selectivity throughout the block (Figures S4 and S5). There were no differences between prosaccade and antisaccade neurons (Figures S6 and S7).

The differences in the maintenance of task selectivity between PFC and ACC neurons seemed to be partly related to a different onset pattern of task selectivity. The population of PFC neurons showed a fairly constant onset of task selectivity at around 350 ms prior to peripheral stimulus onset, whereas the population of ACC neurons displayed a gradual increase in the onset of task selectivity over the block of trials. We confirmed these differences by determining the onset time of significant differences in task selectivity for each neuron in the six sub-blocks of five trials with a bootstrap analysis (see Experimental Procedures). PFC neurons exhibited similar onset times for the six sub-blocks, with a slight trend toward earlier onset times in task selectivity as the blocks progressed (Figure 4B, left). In contrast, task selectivity started progressively later in ACC neurons over the block (Figure 4B, right). In addition, the number of cells discriminating between pro- and antisaccade trials remained at around 80% in the PFC but dropped from about 80% to ~55% in the ACC. A repeated-measures ANOVA on the onset times in the six sub-blocks showed no main effect for PFC neurons [$F(5,250) = 1.73$; $p = 0.13$] but a significant main effect for ACC neurons [$F(5,225) = 6.26$; $p < 0.00005$]. Both monkeys showed a similar pattern of task selectivity throughout the block (Figures S5 and S6; Note 3). There were no differences between prosaccade and antisaccade neurons (Figures S6 and S7).

We also computed task selectivity and onsets of task selectivity for ACC and PFC neurons in the five correct trials immediately before a task switch (black lines in Figures 4B and 4C). The level of task selectivity dropped in the PFC and increased in the ACC following a task switch (Figure 5A). No differences in task selectivity were observed between ACC and PFC neurons in the trials 6 to 30 following a task switch. Likewise, the onset of task selectivity started later in the PFC and earlier in the ACC following a task switch (Figure 5B). This pattern reversed toward the end of a block, with an earlier onset of task selectivity in the PFC than the ACC from trials 16 to 30.

The need to switch to the other task was conveyed to the monkeys by the omission of reward. The first trials in a new block were therefore always error trials. To compare the effect of performance on task selectivity in the PFC and ACC, we computed ROC values for error trials, correct trials that followed an error trial, and correct trials that followed a correct trial (see Experimental

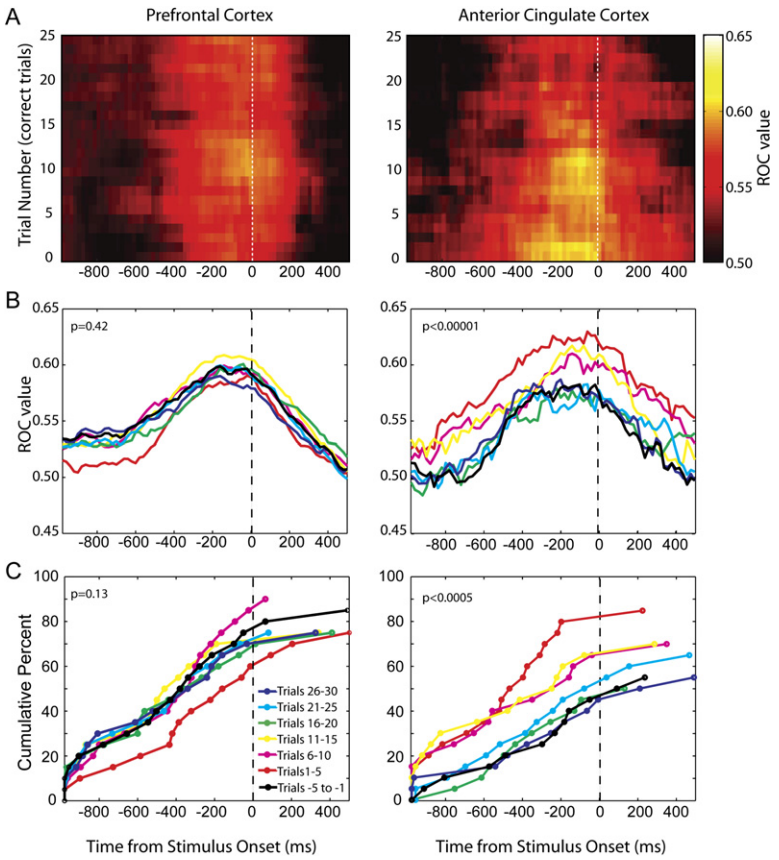

Figure 4. Changes in Task Selectivity in Prefrontal Cortex and Anterior Cingulate Cortex following a Task Switch

(A) Population selectivity (ROC values, color scale) in prefrontal cortex (left) and anterior cingulate cortex (right) as a function of correct trials after a task switch.

(B) Population selectivity (ROC values) in prefrontal cortex (left) and anterior cingulate cortex (right) in sub-block before and after a task switch.

(C) Cumulative distribution of onset times of task selectivity in 51 PFC (left) and 46 ACC neurons (right) as a function of correct trials after task switch. Figure labels for (B) and (C) are in (C) (left panel). Significance values indicate the main effect of repeated-measures ANOVAs with the six sub-blocks following a task switch as the within-subjects factor.

Procedures). We included all error trials and all correct trials in this analysis. A large number of the errors, however, occurred following a task switch (Figure S1). Figure 6 shows that task selectivity was low on error trials in the PFC (left panel, red line) and the ACC (right panel, red line). On the next correct trial following a task switch, task selectivity was still low in the PFC (left panel, blue line) but showed a strong increase in the ACC (right panel, blue line). The differences in task selectivity between error trials and correct trials following an error were not significant in the PFC (paired t test, $p = 0.54$) but they were significant in the ACC (paired t test, $p < 0.0002$). Trials that followed a correct trial showed a strong task selectivity in the PFC (left panel, green line) and ACC (right panel, green line). Task selectivity was different between correct trials that were preceded by an error trial and correct trials that were preceded by a correct trial in the PFC (paired t test, $p < 0.0000005$) but not the ACC (paired t test, $p = 0.97$). The same pattern was observed for both monkeys (Figure S8; Note 2).

DISCUSSION

An influential model of cognitive control proposes that the anterior cingulate cortex monitors conflict during stimulus processing and response selection and recruits the prefrontal cortex during preparatory periods for top-down control processes (Hopfinger et al., 2000; Miller and Cohen, 2001). This model is largely based on human fMRI studies. To date, a single study has compared the response properties of single PFC and ACC neurons (Niki and Watanabe, 1979). Here, to our knowledge, we report the first systematic comparison of preparatory activity in PFC and ACC neurons while monkeys performed a task-switching paradigm. We found that the level of task selectivity was significantly higher in ACC than in PFC neurons during the preparatory period on trials immediately following a task switch. Moreover, ACC neurons exhibited a significant level of task selectivity during the preparatory period on the first correct trial following a response error that was absent in PFC neurons. Taken together, these findings demonstrate that task-selective differences in preparatory neural activity in the ACC lead those in the PFC following a task switch and response errors.

The conflict-monitoring hypothesis (Botvinick et al., 2001) is an influential model that has been proposed to account for the relative roles of different brain areas in the implementation of cognitive control. This model has been supported by fMRI studies that have shown increased levels of activity in the ACC during tasks such as the Stroop task (Carter et al., 2000), which engender conflict by coactivating incompatible response processes. More specifically, conflict monitoring proposes the ACC acts as a conflict detector and recruits the PFC to engage

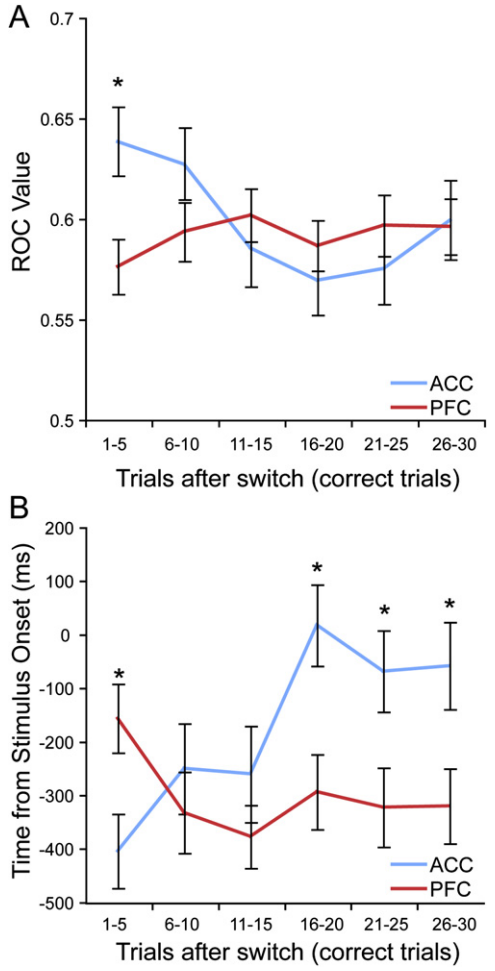

Figure 5. Changes in Task Selectivity and Onset of Task Selectivity in Prefrontal Cortex and Anterior Cingulate Cortex following a Task Switch

(A) Mean ± standard error of the mean task selectivity of prefrontal cortex neurons (red) and anterior cingulate cortex neurons (blue) as a function of correct trials after a task switch.

(B) Mean ± standard error of the mean onset of task selectivity of prefrontal cortex neurons (red) and anterior cingulate cortex neurons (blue) as a function of correct trials after a task switch.

*$p < 0.05$ (t test).

control mechanisms (van Veen et al., 2001; Kerns et al., 2004). A prediction of this model is that the PFC is activated during preparatory periods, whereas the ACC monitors for conflict during stimulus processing and response selection (Hopfinger et al., 2000; Miller and Cohen, 2001). What appears to be a clear double dissociation was demonstrated by MacDonald and colleagues with a Stroop task (MacDonald et al., 2000). In their event-related fMRI study, the PFC was more active during the preparatory period of the print-color-naming condition than the word-reading condition but did not show any differences during the response period. By contrast, the ACC was more active during the response period when subjects were required to name the print colors in the incongruent condition. These studies lead the authors to conclude that the PFC provides top-down bias signals while the ACC is involved in conflict monitoring. Two monkey electrophysiology studies that searched specifically for conflict signals in the ACC have failed to identify those signals (Ito et al., 2003; Nakamura et al., 2005). Our findings of differences in the task-preparation period between prosaccade and antisaccade trials in both PFC and ACC neurons are also not consistent with this model.

The findings reported here suggest that both the PFC and ACC participate in top-down control processes. Several fMRI studies have also reported task-related preparatory activation in the ACC (Ford et al., 2005; Luks and Simpson, 2004; Luks et al., 2002; Wiese et al., 2004) and even MacDonald et al. (2000) found increased, though non-task-specific, activation in the ACC during the preparatory period. Preparatory activity in ACC neurons has also been reported by Shima and Tanji in a task in which monkeys had to decide to either push or turn a handle based on the relative amount of reward delivered for each response (Shima and Tanji, 1998). About one-third of ACC neurons showed preparatory activity in this task. We therefore propose that the role of the ACC is not limited to error detection or performance monitoring but rather that this area might be more generally recruited when cognitive control must be engaged to successfully deal with increased task demands as imposed, in this case, by a task switch.

The strongest direct support for this hypothesis comes from our finding of differences in the pattern of task selectivity between the PFC and ACC following erroneous responses. Performance errors were associated with low task selectivity in both areas. However, ACC neurons displayed a significant increase in task selectivity on the first correct trial following an error trial, which was not present in PFC neurons. Such a finding is at odds with a strict conflict-monitoring interpretation, which would suggest that performance errors should result in an increased ACC signal that would be passed on to the PFC to engage greater control on the next trial. Our data suggest an alternative explanation; that the ACC is selectively engaged to enhance cognitive control in response to increases in task difficulty. This conceptualization is more consistent with the error likelihood model of ACC function in which the ACC predicts task demands and recruits cognitive control based on the probability of making a response error in a given behavioral context (Brown and Braver, 2005).

In the present study, monkeys were not cued in advance as to when a task switch would occur, and the animals' error rates prior to a task switch do not suggest that the monkeys anticipated the switch (Figure 1C). Instead, the need to switch to the alternate task was conveyed to the monkeys by withholding the juice reward until they performed the alternate task correctly. Therefore, one might hypothesize that the increased task selectivity following a task switch is not specifically related to task switching but might reflect a more general role of the

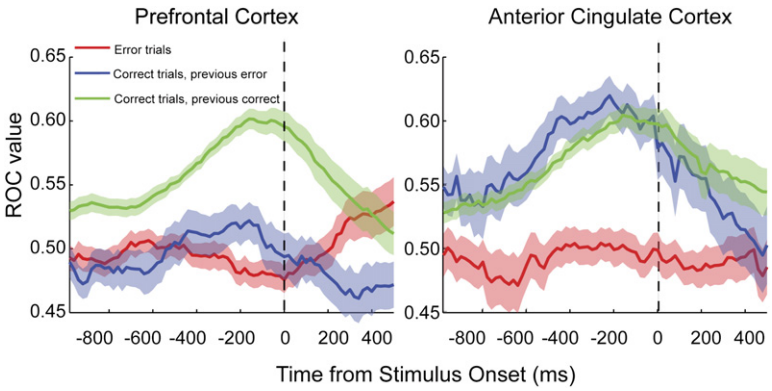

Figure 6. Effects of Performance on Task Selectivity in Prefrontal Cortex and Anterior Cingulate Cortex

Task selectivity in prefrontal cortex (left) and anterior cingulate cortex (right) on error trials (red), correct trials that followed an error trial (blue), and correct trials that followed a correct trial (green). Solid lines indicate mean task selectivity, and envelopes indicate standard error of the mean. Anterior cingulate cortex neurons showed an increase in task selectivity following an error trial.

ACC in the anticipation of conflict, i.e., in this case between an anticipated and received reward. This hypothesis, however, would predict an overall increase in ACC activation following an unrewarded trial irrespective of whether it was a prosaccade or antisaccade trial. In our analysis, we found that task selectivity, i.e., differences in neural activity between pro- and antisaccades, increased following a task switch. These data suggest that neurons in the ACC but not in the PFC increase their task selectivity in situations that require an increase in cognitive control. While we cannot rule out the possibility that the pattern of task selectivity we observed in ACC neurons following a task switch was the result of conflict induced by competition between the previously rewarded and current task sets (Allport et al., 1994), the fact that this selectivity was observed during the preparatory period is inconsistent with a circumscribed conflict-monitoring function and more consistent with an enhanced role of the ACC in demanding task situations. This conceptualization fits with a hypothesized role of the ACC in top-down control that is separate from the PFC (Cohen et al., 2000), although the selective nature of the activity we observed suggests that this is a selective rather than a general preparatory mechanism.

The finding that ACC neurons did not show any significant differences in task selectivity between correct trials that followed an error and correct trials that followed a correct response indicates that task selectivity in the ACC does not immediately decrease when the PFC is activated. In fact, ACC neurons showed significant, although reduced, task selectivity even at the end of a task block. Our data therefore suggest that ACC neurons are also involved in the maintenance of task set. A role of ACC neurons in task maintenance is consistent with the results of a recent study that demonstrated that ACC lesions did not impair monkeys' ability to switch between behavioral alternatives, but did impair their ability to sustain the correct behavior following a task switch (Kennerley et al., 2006). Evidence from fMRI studies investigating task switching in human subjects is also consistent with such a role (Dosenbach et al., 2006).

fMRI studies of conflict monitoring have suggested that the ACC does not play a direct role in top-down control but rather sends conflict-related information to the PFC, which is responsible for engaging control processes (Botvinick et al., 1999; MacDonald et al., 2000). Our findings of enhanced response selectivity during the preparatory period in ACC neurons, coupled with enhanced ACC selectivity following erroneous responses, suggest a role of the ACC in top-down control. This contention is supported by anatomical evidence that has shown that the ACC is connected to a number of brain areas known to be involved in generating motor responses. For example in the oculomotor system, the ACC is known to project to both the superior colliculus (SC) (Leichnetz et al., 1981) and frontal eye fields (Wang et al., 2004). Based on our results, we propose that both the PFC and ACC are involved in top-down control processes (Figure 7). The consistent pattern of task selectivity we observed in PFC neurons is consistent with a role of the PFC in maintenance of task

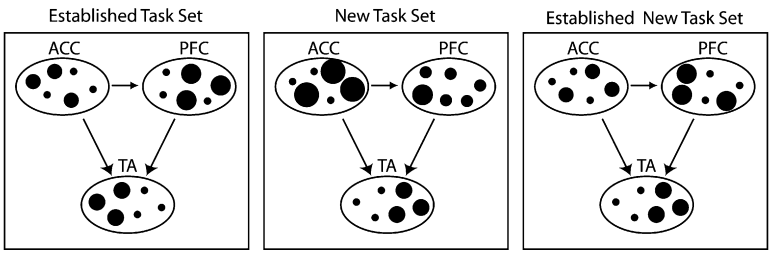

Figure 7. Schematic Representation of Preparatory Activity in a Population of Anterior Cingulate Cortex and Prefrontal Cortex Neurons before and after a Task Switch

Each dot represents an individual neuron, and the size of the dot indicates relative discharge rate. A subpopulation of ACC and PFC neurons is activated during performance of a given task. When the task switches, a different subpopulation of task-selective neurons is strongly activated in the ACC, whereas the population of PFC neurons initially shows weak task selectivity. After several trials, task selectivity decreases in the ACC and increases in the PFC during the preparatory period. Whether task-selective ACC neurons directly activate target areas (TA) or recruit PFC neurons is not yet known.

rules (Miller and Cohen, 2001), and we have recently shown that PFC neurons send task-related information directly to the SC (Johnston and Everling, 2006). The enhanced selectivity we observed in ACC neurons during difficult task periods may also serve to modulate the activity of target structures in accordance with task demands. Based on the strong connectivity between the ACC and PFC (Bates and Goldman-Rakic, 1993; Paus et al., 2001; Wang et al., 2004), it seems possible that enhanced ACC selectivity recruits PFC neurons, and both structures may act together in a top-down fashion to modulate the activity of other target structures. Further electrophysiological studies are required to determine whether ACC neurons with task-selective activity recruit PFC neurons in situations of increased conflict as suggested by fMRI studies (Kerns et al., 2004) or whether these neurons directly modulate the activity in such task-specific target areas as the SC.

EXPERIMENTAL PROCEDURES

Data were collected from two *Macaca mulatta* (6.5 and 8 kg). All methods described (Desouza and Everling, 2004) were in accordance with the guidelines of the Canadian Council on Animal Care policy on the use of laboratory animals and a protocol approved by the Animal Use Subcommittee of the University of Western Ontario Council on Animal Care.

Task

Each trial began with the presentation of a fixation spot at the center of the screen. Monkeys were required to fixate it within a 0.5° × 0.5° window for a random period of 1100–1400 ms. A visual stimulus (0.15°) was then presented pseudorandomly with equal probability 8° to the left or 8° to the right of the fixation spot. To receive a reward, monkeys had to generate a saccade within 500 ms to the stimulus on prosaccade trials or away from the stimulus to its mirror location on antisaccade trials (5° × 5°). After 30 correct responses, the task switched (e.g., from prosaccades to antisaccades) without any explicit signal to the monkeys (see Everling and Desouza, 2005, for details). Eye movements were recorded at 1000 Hz using a magnetic search coil technique (David Northmore Inst., Newark, Delaware). Monkeys performed between 4 and 20 task switches (median 12) of alternating blocks of pro- and antisaccade trials.

Recording Methods

Neuronal activity was recorded extracellularly from the lateral prefrontal cortex (left hemisphere in monkey W, right hemisphere in monkey R) and anterior cingulate cortex (right hemisphere in both animals) (see Figure S9). Recording chambers were implanted stereotaxically based on images obtained through magnetic resonance imaging. The location of the implanted recording chambers was visualized in situ by MRI. Arrays of two to six dura-puncturing microelectrodes (FHC Inst., Bowdoinham, ME) were individually driven within a recording chamber by either custom-designed screw mini-microdrives that were attached to a delrin grid inside the recording chamber or a computer-controlled multielectrode microelecrode drive (NAN, Plexon Inc, Dallas, TX). To ensure a relatively unbiased sampling of PFC and ACC neural activity, neurons were not prescreened for task-related responses. Instead, we advanced the electrodes until the activity of one or more neurons was well isolated, following which data collection commenced. Waveforms were digitized, stored, and sorted off-line using principal-component analysis in 2D and 3D (Plexon, Dallas, TX).

Data Analysis

Trials associated with errors such as broken or incorrect fixation, failure to generate a saccade within 500 ms, and incorrect responses (e.g., prosaccade on antisaccade trial or vice versa) were excluded from all analyses of neural activity.

Task selectivity was assessed using t tests to compare the mean activity of each neuron on prosaccade and antisaccade trials within a 500 ms epoch immediately preceding presentation of the peripheral stimulus. t tests were evaluated at an alpha level of $p < 0.05$ (see Note 1).

To examine the time course of task selectivity, we performed Receiver Operating Characteristic analyses using a sliding 250 ms time window that was incremented in 20 ms steps for each of the task-selective ACC and PFC neurons (Everling and Desouza, 2005; Wallis and Miller, 2003).

To examine the onset of task-selective activity over the course of trials within a block, ROC values were calculated for each neuron (sliding 250 ms time window, incremented in 20 ms steps) across a five-trial window, slid in one (for Figure 4A) or five-trial steps (for the statistical tests) over the 30 correct trials after a task switch. For each neuron, the activity on correct prosaccade trials was compared with the activity on correct antisaccade trials. All blocks were collapsed for this analysis. The onset of significant task selectivity in each of the six five-trial sub-blocks was determined for each neuron using a bootstrap analysis by repeating each ROC analysis 1000 times for each time point and assigning a condition at random to each trial. The 95th percentile indicated the 5% significance criterion (see Note 3). Differences in onset time for the six sub-blocks were assessed for the populations of task-selective ACC and PFC neurons using one-way repeated-measures ANOVAs (see Note 4). Differences in task selectivity between the six sub-blocks were evaluated using one-way repeated-measures ANOVAs on the mean selectivity in the window 1000 ms before to 500 ms after stimulus onset. All ANOVAs were evaluated at $p < 0.05$.

Supplemental Data

The Supplemental Data for this article can be found online at http://www.neuron.org/cgi/content/full/53/3/453/DC1/.

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